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Outcomes of Burkitt lymphoma with bone marrow involvement or Burkitt leukemia in Chinese children

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ABSTRACT

Importance: Burkitt lymphoma with bone marrow involvement and Burkitt leukemia behave aggressively. Thus far, there are limited data concerning survival and toxicity in Chinese children with Burkitt lymphoma or Burkitt leukemia who have undergone treatment with the non-Hodgkin's lymphoma Berlin-Frankfurt-Münster-90/95 (NHL-BFM-90/95) protocol.

Objective: To analyze outcomes and toxicity in pediatric patients who exhibit Burkitt lymphoma with bone marrow involvement or Burkitt leukemia following treatment with the NHL-BFM-90/95 protocol.

Methods: Patients aged <18 years with bone marrow involvement/leukemia who were treated with the NHL-BFM-90/95 protocol, with or without rituximab, in Sun Yat-Sen University Cancer Center from April 2004 to December 2018 were included in this retrospective analysis.

Results: Twenty-five patients were eligible. Burkitt lymphoma with bone marrow involvement and Burkitt leukemia were present in 10 and 15 patients, respectively. Central nervous system infiltration was not observed in any patients. All patients underwent chemotherapy involving NHL-BFM-90/95 protocol. Six courses of treatment were administered to each patient (v-AA-BB-CC-AA-BB-CC). The BFM-90/95 plus rituximab protocol was administered to 13 patients. The median follow-up interval was 31.9 months (range, 2.5–158 months). Of the 25 patients, four died: three died of tumor progression and one died of therapy abandonment after relief of tumor lysis syndrome. The estimated 5-year event-free survival and overall survival rates were both 85.8% ± 5.0%.

Interpretation: Chinese pediatric patients who exhibit Burkitt lymphoma with bone marrow involvement or Burkitt leukemia can achieve optimal treatment outcomes and exhibit good tolerance when using the NHL-BFM-90/95 protocol.

KEYWORDS
Burkitt lymphoma, Bone marrow, Burkitt Leukemia, B-Cell, Prognosis

INTRODUCTION

Burkitt lymphoma is one of the most common subtypes of pediatric non-Hodgkin's lymphoma (NHL). The most frequently involved areas include the abdomen, lymph nodes, and maxillofacial region; notably, Burkitt lymphoma rarely affects bone marrow. Approximately 20% of patients with Burkitt lymphoma have sporadic bone marrow involvement.[1,2]

Advanced mature B-cell non-Hodgkin's lymphoma (≥25% bone marrow blasts and/or central nervous system involvement) is a highly aggressive tumor.[1] Burkitt lymphoma with bone marrow involvement is classified

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as stage IV mature B-cell non-Hodgkin's lymphoma, while Burkitt lymphoma with ≥25% blasts in the bone marrow is defined as Burkitt leukemia. Notably, Burkitt lymphoma with 5%–25% blasts in the bone marrow is classified as Burkitt lymphoma with bone marrow involvement. The prognosis is good and most patients (including those with advanced disease) achieve lifelong complete remission.[3] Occasionally, successful treatment requires a collaborative effort between chemotherapy and intensive care unit teams in Chinese hospitals. More than 20 years ago, patients with Burkitt leukemia who received long-term chemotherapy had dismal outcomes. Sun Yat-Sen University Cancer Center is one of the locations that first applied the protocols of the Berlin-Frankfurt-Münster (BFM) International Cooperative Group for treatment of pediatric patients with Burkitt lymphoma in China.[4] In the present study, we investigated the outcomes and characteristics of pediatric patients who received treatment with the BFM protocol, with or without rituximab, for Burkitt lymphoma with bone marrow involvement.

METHODS

Ethical approval

The present study was approved by the Ethics Board of the Sun Yat-sen University Cancer Center (B2019-199-01) and conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from the parents or legal guardian of each patient.

Eligibility and evaluation

Confirmed diagnosis was established using a combination of histopathologic and molecular analysis methods. This study included pediatric patients (age <18 years) with Burkitt lymphoma involving bone marrow infiltration (Figure 1) who were newly diagnosed and treated with the NHL-BFM-90/95 protocol from April 2004 to December 2018. Patients with ≥5% bone marrow blasts were considered to have bone marrow-positive Burkitt lymphoma. Flow cytometry analysis showed that blasts in bone marrow typically expressed well known monotypic surface IgM, pan-B-cell antigens (e.g., CD19, CD20, CD22, and CD79a), and kappa or lambda, but not CD5, CD23, Bcl-2, CD138, or TdT. Patients with 5%–25% bone marrow blasts were considered to have Burkitt lymphoma with bone marrow involvement; those with ≥25% bone marrow blasts were considered to have Burkitt leukemia. Patients with primary immunodeficiency, primary tumors, or prior chemotherapy treatments were excluded from the analysis. All medical records were extracted from the hospital's electronic database and retrospectively reviewed. Severity was evaluated using Murphy Staging. The date of last follow-up was February 1, 2019. All original data were deposited on http://www.researchdata.org.cn (RDD number RDDA2019001318).

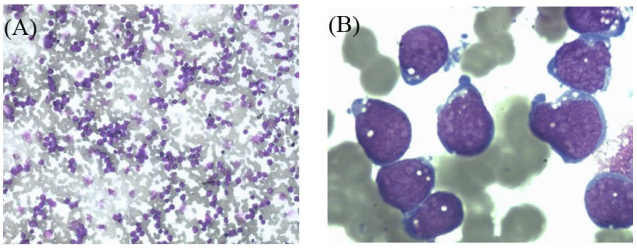

FIGURE 1 Bone marrow hyperplasia was substantial. Tumor cells with round nuclei were characterized by multiple visible vacuoles. These lymphoma cells displayed both thick chromatin and cytoplasm with a rich dark blue stain (A, 10 × 10; B, 10 × 100; H & E stain).

Treatment

All patients with Burkitt lymphoma received stratified treatment in accordance with the modified BFM 90/95 protocol, using the current version adapted for Chinese patients. The chemotherapy plan is shown in Table S1 and treatment stratification is shown in Table S2. All patients with lactate dehydrogenase (LDH) >1000 U/L were assigned to the high-risk group (R4) and treated with the NHL-BFM-90/95 protocol. Patients with LDH <1000 U/L were considered high-risk (R4) before 2017 and received six courses of v-AA-BB-CC-AA-BB-CC combined with rituximab in our center, in accordance with the modified BFM-90/95 protocol.[5] In contrast, these patients were assigned to the R3 group after 2017; they received five courses of the above treatment. Twelve patients did not receive rituximab, primarily for economic reasons. The remaining patients received rituximab at a dose of 375 mg/m^2 on day 0, prior to each course of chemotherapy; intrathecal methotrexate and cytarabine were concurrently administered during each course.[2] Chemotherapy was scheduled at 3-week intervals after hematopoietic reconstitution had been achieved. All patients were evaluated before initiation of chemotherapy. Patients at risk of tumor lysis were transferred to the intensive care unit prior to central catheter placement; they received chemotherapy with close monitoring of electrolytes, uric acid, urinary volume, and urinary crystals. Hemodialysis or rasburicase was used to treat tumor lysis syndrome (TLS); patients were transferred from the intensive care unit to the general ward for subsequent chemotherapy following relief of TLS. The response to chemotherapy was evaluated after every second course by imaging work-up and bone marrow aspiration. Toxicities/adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE, v.4.03, National Cancer Institute, 2010).[6]

Statistical methods

Overall survival was calculated from the beginning of treatment until death from any cause or last follow-up. Event-free survival (EFS) was defined as the interval

between the beginning of treatment until treatment failure, death, treatment discontinuation for any reason, or detection of second neoplasm. The overall survival and EFS were calculated with the Kaplan–Meier method by using SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). Differences between groups were compared by the log-rank test. All tests were two-tailed and $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

This study initially included 189 patients with Burkitt lymphoma who were treated with the NHL-BFM-90/95 protocol at our institution. After application of exclusion criteria, 25 patients (19 boys and six girls; median age, 8 years [range, 2–17 years]) who exhibited Burkitt lymphoma with bone marrow involvement or Burkitt leukemia were enrolled. Primary sites predominantly included the abdomen, neck, or mediastinum. Central nervous system infiltration was not observed in any patients (Table 1). Chromosomal rearrangement at MYC (8q24) was detected on tumor specimens using a dual-color MYC/IGH translocation probe designed to detect t(8;14)(q24.1;q32). All patients exhibited MYC rearrangement. The median serum uric acid level at initial diagnosis was 504 μmol/L (range, 117–1509 μmol/L; normal range, 142–416 μmol/L) (Table 1). Notably, the serum uric acid level was elevated in the five patients with TLS (peak value, 1317 μmol/L). Rasburicase was administered to the remaining 20 patients following catheter placement for prophylaxis of TLS. Ten patients exhibited Burkitt lymphoma with bone marrow involvement and 15 patients exhibited Burkitt leukemia. There were no significant differences in clinical characteristics (e.g., age, sex, LDH level, and response to the initial two courses of treatment) between patients who exhibited Burkitt lymphoma with bone marrow involvement and those who exhibited Burkitt leukemia. Of the 15 patients with Burkitt leukemia, nine had 25%–89% bone marrow blasts and six had >90% bone marrow blasts. Rituximab combined with BFM-90/95 protocols was administered to 13 patients in the R4 group. Of the 13 patients treated with rituximab, nine had Burkitt leukemia and four had Burkitt lymphoma with marrow involvement. The 12 patients who did not receive rituximab included six with leukemia and six with bone marrow involvement. The median follow-up interval was 31.9 months (range, 2.5–158 months). Sixteen of the 25 patients had an elevated LDH level (1049.8–22557.0 U/L) at initial diagnosis. The primary tumor site was the abdomen in 18 of the 25 patients. The remaining patient demographics and disease characteristics are summarized in Table 1.

TABLE 1 Patient characteristics prior to treatment

Features	Number of patients (n = 25)
Age (years)	8 (2–17)
Serum uric acid (μmol/L)	504 (117–1509)
Sex	
Male	19
Female	6
Bone marrow involvement	
5%–24%	10
25%–89%	9
≥90%	6
LDH (U/L)	
<500	7
500–999	2
≥1000	16
Primary tumor site	
Neck or mediastinum	7
Abdomen	18
Mesenterium	1
Ileocecus	5
Kidney	5
Pelvis	7
Central nervous system	0
Rituximab	
Yes	13
No	12
Response to initial two courses of chemotherapy	
CR	23
PR	1
unknown	1
Tumor lysis syndrome	
Yes	5
No	20

Data are shown as n or median (range). LDH, lactate dehydrogenase; CR, complete response; PR, partial response.

Outcome

Twenty-one patients achieved continuous complete remission and were alive at the last follow-up. However, four patients died: three exhibited tumor progression between 3 and 18 months after initiation of chemotherapy, while one abandoned therapy after TLS had been relieved within 2.5 months after the initiation of chemotherapy. The estimated 5-year EFS and overall survival rates were both 85.8% ± 5.0%. Pediatric patients who exhibited Burkitt lymphoma with bone marrow involvement or Burkitt leukemia and were treated using BFM-90/95 protocols plus rituximab achieved overall survival outcomes similar to those of patients who received treatment without rituximab (84.6% ± 10.0% vs. 82.5% ± 11.3%, log-rank $\chi^2 = 0.12$, $P = 0.91$). Patients were stratified according to rituximab treatment status, as follows: group 1 included

patients with bone marrow involvement who received rituximab, group 2 included patients with bone marrow involvement who did not receive rituximab, group 3 included patients with leukemia who received rituximab, and group 4 included patients with leukemia who did not receive rituximab. The 5-year EFS rates of groups 1, 2, 3, and 4 were 75.0%, 83.3%, 88.9%, and 83.3%, respectively (Table 2).

Safety

There were no instances of toxic death among the 25 patients in this study. TLS occurred in five patients and involved oliguria, vomiting, crystalluria, and deteriorated renal function during the initial course of chemotherapy (prephase V). TLS was confirmed by the presence of hyperuricemia, hyperkalemia, and hyperphosphatemia in laboratory examinations. Patients with uric acid > 428 mmol/L were administered rasburicase for prophylaxis of TLS; three of these patients required hemodialysis. Twenty-four patients had Grade 4 hematological toxicity at the end of course V-RAA (Table 3); they were treated with granulocyte colony-stimulating factor. Subsequent chemotherapy was administered following recovery of hematological function. None of the patients required delayed chemotherapy due to hematological toxicity.

DISCUSSION

Burkitt lymphoma is an aggressive mature B-cell lymphoma that constitutes one-third of non-Hodgkin lymphomas in patients younger than 14 years of age.[7] Although the biological and clinical behaviors of Burkitt lymphoma in pediatric patients are malignant and the disease develops rapidly, its long-term outcomes are favorable. The most commonly involved regions include the abdomen, peripheral lymph nodes, neck, mediastinum, and kidney.[8] Sporadic bone marrow involvement is present in approximately 20% of patients with Burkitt lymphoma.[1] Our findings showed bone marrow involvement in 13.2% of patients (25/189), which was slightly lower than the rate in the previous report. This difference might be related to the confirmed diagnosis and treatment before bone marrow involvement occurred among most patients with Burkitt lymphoma. Our findings support the notion that Burkitt lymphoma in pediatric patients is an highly aggressive lymphoma with sporadic bone marrow involvement.[9]

TABLE 2 Survival characteristics of patients stratified according to rituximab treatment status

Characteristics		Number of patient	EFS (%)
Bone marrow involvement			
Group 1	Rituximab	4	75.0 ± 21.7
Group 2	No rituximab	6	83.3 ± 15.2
Leukemia			
Group 3	Rituximab	9	88.9 ± 10.5
Group 4	No rituximab	6	83.3 ± 15.3

EFS, event-free survival.

TABLE 3 Adverse events with severity grade ≥3

Toxicity	Grade 3, *n* (*n*/*N*)	Grade 4, *n* (*n*/*N*)
Febrile neutropenia	6 (6/25)	19 (19/25)
Mucositis	12 (12/25)	5 (5/25)
Liver function impairment	16 (16/25)	3 (3/25)
Elevated creatinine	2 (2/25)	3 (3/25)

In our center, Burkitt lymphoma with bone marrow involvement arose from the abdomen in 18 of 25 pediatric patients, similar to results in other developed countries where Burkitt lymphoma or Burkitt leukemia was present in the abdomen in approximately 60% of patients.[10,11] Furthermore, a study in Central America showed that the abdomen comprised the primary site in 68.1% of patients.[9]

Some centers in advanced areas in China have employed BFM-90/95 protocols to treat pediatric patients with Burkitt lymphoma since the 1990s; this has led to overall survival improvement from 30% to 85%. The biological behaviors of Burkitt lymphoma and Burkitt leukemia are quite different from those of acute lymphoblastic leukemia; notably, mature B-cell lymphomas are highly aggressive and develop rapidly. The survival rate in patients with mature B-cell lymphoma was only 34% using long-course chemotherapy suitable for lymphoblastic lymphoma.[4] Chemotherapy with risk-stratification, short duration, and pulse treatment based on biological behavior has been associated with favorable outcomes.[12,13] The 5-year overall survival rate of the 25 pediatric patients in our study was 85.8% ± 5.0%. Chemotherapy with reduced intensity or delayed administration is presumed to have negative impacts on both complete response rate and survival.[14] In the BFM protocol, the first intensive course follows the completion of prophase chemotherapy. Importantly, TLS usually occurs in prephase V; all of our patients were carefully evaluated for TLS risk prior to chemotherapy initiation. Patients with high LDH and uric acid levels were at high risk of TLS; thus, they were administered rasburicase or transferred to the intensive care unit and provided supportive hemodialysis for prophylaxis of TLS, in accordance with a previously published approach.[15] One patient experienced TLS and underwent rescue treatment after prephase V; after he achieved complete response, his parents abandoned further chemotherapy. TLS usually occurs very rapidly and serum potassium can become elevated within hours. If patients are not prepared for hemodialysis, they may have a high risk of death from hyperpotassemia or acute renal failure.[4]

None of our patients died due to chemotherapy toxicity. The most serious toxicity was grade IV bone marrow suppression. The incidence of severe adverse events including grade IV bone marrow toxicity was 100%;

all occurred in the first two cycles of chemotherapy. Other adverse events included mucositis, transient liver dysfunction, and infectious complications, as reported in a previous study.[16] Patients who experienced adverse events were provided supportive treatment with granulocyte colony-stimulating factor and administered broad-spectrum antibiotics for neutropenic fever. In all patients, bone marrow suppression recovered prior to subsequent chemotherapy. Our findings imply that Asian children can tolerate intensive chemotherapy approaches in the context of sufficient supportive treatment.[17] The present study also indicated that the addition of rituximab to the BFM protocol was safe and well tolerated.[18] The 13 patients who received rituximab had no signs of rituximab allergy following the use of a pre-treatment conditioning regimen.[19] They all had persistent hypogammaglobulinemia after completion of chemotherapy.

Patients who received BFM combined with rituximab treatment exhibited survival similar to that of patients who received BFM alone.[20] The EFS rates were comparable between patients who received rituximab-containing therapy and those who did not, among patients who exhibited Burkitt lymphoma with bone marrow involvement and those who exhibited Burkitt leukemia. However, this study was limited to a retrospective design and did not involve randomization. Therefore, our study had insufficient power to explain the role of anti-CD20 antibody treatment in outcomes of patients with Burkitt lymphoma and those with Burkitt leukemia. An international randomized phase III trial showed that the addition of rituximab to standard therapy increased the EFS rate for high-risk patients.[21] Hence, we suggest that all high-risk patients receive rituximab if they are not restricted by economic factors.

There were some limitations in our study. First, it used a retrospective design and small sample size. Therefore, the range of survival outcomes was considerable and may have been subject to various biases. Second, the presence of minimal residual disease was not monitored after completion of chemotherapy. Notably, long-term chemotherapy, as applied to patients with acute lymphoblastic leukemia, was used for very few patients with Burkitt leukemia more than 10 years ago; it was ineffective in those studies.[4] Third, our study included a small group of patients with stage IV Burkitt lymphoma who did not exhibit central nervous system involvement. Fourth, few patients were treated with other protocols or exhibited disease without bone marrow involvement; thus, comparisons among groups were relatively weak. Finally, rituximab treatment was not randomly assigned and our study did not have sufficient power to determine the role of rituximab in patient outcomes.

In conclusion, the present study demonstrated that pediatric patients who exhibit Burkitt lymphoma with bone marrow involvement and those who exhibit Burkitt leukemia can achieve positive outcomes using the BFM-NHL protocol as first-line treatment. Toxicity can be appropriately managed before subsequent chemotherapy in Chinese pediatric patients, although patients at high risk of TLS should be treated cautiously. Importantly, the addition of rituximab to the BFM protocol is safe and well tolerated.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

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